REMARKS

These remarks are in response to the Office Action mailed May 31, 2000. Claims 1 to 11 are pending. Claims 3 to 11 stand withdrawn from consideration as being directed to a non-elected invention. By the present amendment, new claims 12 and 13 have been added. Accordingly, upon entry of the amendment, claims 1, 2, 12 and 13 are under examination.

Regarding the Deposited Biological Material

Submitted herewith as Appendix A, is a declaration for the biological deposit disclosed in the specification at page 8, and copies of the Deposit Receipt in English and in Japanese. The declaration, executed by an authorized representative of the assignee of the above-identified application, indicates that the biological deposit conforms with the requirements for depositing biological material under 37 CFR 1.801-1.809. Applicants respectfully request that the declaration and biological deposit receipts be made of record in the application.

Regarding the Amendments and New Claims

The specification has been amended to delete the redundant sequence listing beginning after the claims, numbered pages 1 to 7, in order to comply with the Examiner's request. The amendment was therefore made to address an informality. Accordingly, the amendment to the specification does not add new matter.

Claim 1 has been amended to define the claimed thermophilic enzyme with greater particularity. Support for the amendment can be found, for example, at page 23, middle of the first paragraph, which discloses that the enzyme forms a tetramer. Accordingly, the amendment to claim 1 does not add new matter.

Support for new claims 12 and 13 can be found throughout the specification. In particular, claims 13 and 14 are supported, for example, at page 22, lines 20-25, which discloses the recited amino acids at the recited positions, and at page 3, lines 4-11, which discloses that 1 to 30 or 1 to 18 amino acids of SEQ ID NO:2 can be replaced. Thus, new claims 12 and 13 do not add new matter.

In sum, as the amendment to claim 1 and new claims 12 and 13 do not add new matter Applicants respectfully request entry thereof. Applicants respectfully request reconsideration of the present application.

I. OBJECTION TO THE SPECIFICATION

The specification stands objected to for including two identical sequence listings. The Patent Office requests cancellation of one of the listings.

As set forth above, the specification has been amended to delete the redundant sequence listing beginning after the claims and numbered pages 1 to 7. Accordingly, in view of the amendment to the specification, Applicants respectfully request withdrawal of the objection to the specification.

II. REJECTIONS UNDER 35 U.S.C. §112, FIRST PARAGRAPH

The rejection of claims 1 and 2 under 35 U.S.C. §112, first paragraph, as allegedly lacking enablement is respectfully traversed. The Patent Office indicates that "the specification, while being enabling for SEQ ID NO:2," allegedly "does not reasonably provide enablement for its variants wherein a plurality of amino acid residues are mutated." In particular, the specification allegedly "does not specify these variant structural limitations which can have a plurality of amino acids within SEQ ID NO:2, mutated" and furthermore, allegedly "one of skill in the art has to go through the burden of undue experimentation in order to recognize such SEQ ID NO:2 variants among the numerous enzymes having glycosidase activity."

Applicants submit that claims 1 and 2, prior to the present amendment, are adequately enabled by the specification. Nevertheless, solely in order to further prosecution of the subject application, claim 1 has been amended, which amendment is believed to overcome the grounds for rejection. Accordingly, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. §112, first paragraph.

Notwithstanding the foregoing, Applicants make the following remarks of record relating to the grounds for rejection under 35 U.S.C. §112, first paragraph. The following remarks may also pertain to one or more of new claims 12 and 13 and, as such, the remarks are respectfully requested to be considered by the Examiner.

In order to satisfy the enablement requirement under 35 U.S.C. §112, first paragraph, the specification must describe how to make and use the invention without undue experimentation. In the present case, the specification provides guidance to the skilled artisan to identify thermophilic enzymes having β-glycosidase activity within the scope of the claims without undue experimentation.

For example, the specification discloses that β-glycosidase activity can be assayed by adding a substrate, X-Glu, to a sample containing the enzyme and measuring the amount of absorbance at 620 nm (see, for example, page 12, line 27, to page 13, line 8). Such assays for detecting β-glycosidase activity were also known in the art at the time the application was filed. Thus, in view of the specification, which discloses detecting β-glycosidase enzyme activity, and knowledge in the art, the skilled artisan could readily determine whether a thermophilic enzyme had β-glycosidase activity using a routine assay.

For identifying thermophilic enzymes having β-glycosidase activity that form a tetramer, the specification discloses that gel filtration, an assay well known in the art at the time of the invention, can be used to identify tetramers (see, for example, page 23, lines 15-20). Other assays for determining whether proteins form oligomers, including tetramers, were well known in the art at the time of the invention. For example, non-denaturing gel electrophoresis and sucrose density gradient centrifugation are but two of the many routine assays known in the art for characterizing whether proteins form tetramers.

In sum, in view of the specification and of knowledge in the art at the time of the invention, thermophilic enzymes having the requisite β-glycosidase activity and which form tetramers could be identified using routine assays. Accordingly, clearly the skilled artisan could readily identify enzymes of claims 1 and 2 and new claims 12 and 13 without undue experimentation.

Furthermore, the specification discloses conserved amino acids between SEQ ID NO:2 and several related enzymes (see, for example the sequence alignments in Figure 5). Particular amino acids likely important for enzyme activity inferred by conservation with related enzymes are also disclosed by the specification. For example, the specification discloses that E155 and H111 of BGPh (SEQ ID NO:2) correspond to E206 and H150 of the putative acid/base catalyst in the Sβ-gly molecule, and that E324 and R75 of BGPh correspond to E387, the nucleophile,

and R79 in the spatial proximity of the nucleophile (see also, for example, page 22, first paragraph).

Moreover, the specification discloses structural features within the class of claimed thermophilic enzymes having β-glycosidase activity. For example, the specification discloses two major hydrophobic clusters in BGPh between residues 90 and 265 and 131 and 210 (see page 23, last paragraph, through page 24, second paragraph). The specification additionally discloses that the exposed hydrophobic areas of the clusters may allow hydrophobic substrates to the active site to bind them there (see page 24, lines 19-24). In sum, the specification discloses conserved amino acids, the putative function of specific residues, as well as structural domains (*e.g.*, substrate recognition) that characterize enzymes within the claimed class of thermophilic enzymes having β-glycosidase activity.

Thus, as to the grounds for rejection relating to "no example of variant sequences are provided," the specification teaches how to identify the claimed thermophilic enzymes having the requisite β-glycosidase, which form tetramers and which amino acids are likely to be required for activity. Thus, Applicants need not provide examples for each and every possible sequence within the claims in view of the fact that the specification teaches how to identify thermophilic enzymes having β-glycosidase activity which form tetramers; the conserved features of the claimed enzymes; and the structural features of the claimed enzymes such that the skilled artisan would readily recognize whether a particular thermophilic enzyme was within the scope of the claims.

Accordingly, as to the statement by the Patent Office that the "current state of prior art indicates that any amino acid composition from any source having glycosidase activity needs to have little/if any structural homology to SEQ ID NO:2," Applicants respectfully disagree. Rather, in view of the fact that the specification discloses conserved amino acids shared between SEQ ID NO:2 and related enzymes and sets forth specific amino acids and structural features likely to be important for activity/specificity of the claimed thermophilic enzymes having β-glycosidase activity, the skilled artisan, based on these disclosures, would clearly recognize that enzymes within the class of claimed enzymes would likely have the aforementioned features.

In sum, in view of the guidance in the specification, which teaches how to identify the claimed thermophilic enzymes having β-glycosidase activity and which form tetramers using

routine assays, and which teaches salient structural features of the thermophilic enzymes within the claimed class of enzymes, the skilled artisan would readily be able to make the thermophilic enzymes having β-glycosidase activity without undue experimentation and would also be able to recognize whether a protein was within the claimed class of enzymes.

As a final point, the Patent Office uses an erroneous standard to determine whether experimentation is routine by stating "one of skill in the art has to go through the burden of undue experimentation in order to recognize such SEQ ID NO:2 variants among the numerous enzymes having glycosidase activity." In fact, routine experimentation in the art can include screening of numerous numbers of enzymes. To use the words of the Federal Circuit, enablement is not precluded by screening large numbers of compositions, as long as that screening is "routine," *i.e.*, not "undue." Thus, whether large numbers of compositions (*e.g.*, proteins) may need to be screened is irrelevant to an enablement inquiry.

As the Patent Office correctly notes, the Federal Circuit in In re Wands held that the focus of the enablement inquiry should be whether the experimentation needed to practice the invention is or is not "undue." The court set forth specific factors to be considered.

One of these factors is "the quantity of experimentation necessary." Guidance as to how much experimentation may be needed and still not be "undue" is set forth by the Federal Circuit in, *e.g.*, Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987). In Hybritech, the applicant had claims that were generic to all IgM antibodies directed to a specific antigen. However, only a single antibody-producing cell line had been deposited. The PTO had rejected claims that were generic to all antibodies directed to the antigen as lacking an enabling disclosure.

The Federal Circuit reversed, noting that the evidence indicated that those skilled in the monoclonal antibody art could, using the state of the art and applicants' written disclosure, produce and screen new hybridomas secreting other monoclonal antibodies falling within the genus without undue experimentation. The court ruled that applicants' claims need not be limited to the specific, single antibody secreted by the deposited hybridoma cell line (significantly, the genus of antibodies was allowed even though only one antibody species was disclosed). The court was acknowledging that, because practitioners in that art are prepared to screen large numbers of negatives in order to find a sample that has the desired properties, the

screening that would be necessary to make additional antibody species was not "undue experimentation."

By analogy, those skilled in the art of the present invention recognize that screening large numbers of enzymes to identify a protein having the desired properties may be needed (*i.e.*, the claim limitations of β-glycosidase activity, tetramer formation, SEQ ID NO:2 having a limited number of substitutions, 30 or 18, with conserved amino acids at specified positions, etc.). In this regard, the assays discussed above disclosed by the specification and known in the art used to identify enzymes within the scope of the claims are routine and were all well known in the art at the time the application was filed. Furthermore, in view of the above-discussed guidance in the specification, which discloses structural features of proteins within the claimed class of thermophilic enzymes having β-glycosidase activity, the skilled artisan would readily recognize such enzymes. Thus, those skilled in the art, using Applicants' disclosure and knowledge in the art, could make and identify thermophilic enzymes having β-glycosidase activity within the scope of the claims without undue experimentation. Accordingly, Applicants maintain that the claims, prior to the present amendment, as amended, and new claims 12 and 13, are adequately enabled under 35 U.S.C. §112, first paragraph.

III. REJECTION UNDER 35 U.S.C. §101

The rejection of claims 1 and 2 under 35 U.S.C. §101 as allegedly directed to non-statutory subject matter is respectfully traversed. The Patent Office indicates that the claimed thermophilic β-glycosidase enzymes are "a product of nature and therefore is unpatentable."

Applicants wish to thank the Examiner for pointing out that the claims may have been construed as being directed to non-statutory subject matter. As set forth above, claim 1 has been amended to recite that the claimed β-glycosidase enzymes are "isolated." Accordingly, in view of the amendment, Applicants respectfully request that the rejection under 35 U.S.C. §101, first paragraph be withdrawn.

IV. REJECTIONS UNDER 35 U.S.C. §102(b)

The rejection of claims 1 and 2 under 35 U.S.C. §102(b) as allegedly anticipated by Bylina *et al.* (WO 97/25417) is respectfully traversed. The Patent Office indicates that Bylina

et al. allegedly describe "a thermostable glycosidase enzyme amino acid sequence of which has 85.4% homology . . . . to SEQ ID NO:2 of this invention" obtained from organisms "which grow optimally at 100°C," therefore, allegedly anticipating claims 1 and 2. It is noted that the Patent Office refers to "attached alignment data" to Applicants' SEQ ID NO:2, but no such alignment data was provided with the Office Action.

Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration (In re Spada, 15 USPQ 2d 1655 (Fed. Cir. 1990), In re Bond, 15 USPQ 2d 1566 (Fed. Cir. 1990)).

Claim 1, as amended, recites that the claimed thermophilic enzyme having β-glycosidase activity "forms a tetramer, in which each subunit of the tetramer comprises the amino acid sequence of SEQ ID NO:2." In contrast, as acknowledged by the Examiner, the cited Bylina *et al.* publication does not describe such an enzyme. Thus, as the cited Bylina *et al.* publication does not describe each and every element of claim 1, Bylina *et al.* can not anticipate claim 1 or depending claim 2. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. §102(b) over Bylina *et al.* (WO 97/25417) be withdrawn.

As to new claims 12 and 13, Bylina *et al.* do not describe an enzyme comprising SEQ ID NO:2 having from 1 to 30 or 1 to 18 amino acids replaced in which specified amino acids in SEQ ID NO:2 are retained. Thus, Bylina *et al.* (WO 97/25417) do not anticipate new claims 12 and 13.

The rejection of claims 1 and 2 under 35 U.S.C. §102(b) as allegedly anticipated by Ladrat *et al.* (J. Mar. Biotechnol. 4:192 (1996)) is respectfully traversed. The Patent Office indicates that Ladrat *et al.* allegedly describe "a thermostable beta glycosidase from Pyococcus whose physicochemical properties, such as pH and optimal temperature, are identical to the enzyme claimed instantly." Although the Patent Office acknowledges that "the exact amino acid sequence of glycosidase of Ladrat *et al.* is not disclosed," it anticipates claims 1 and 2 allegedly "because of its identical optimal pH and temperature to the enzyme claimed instantly it is believed to have some homology to SEQ ID NO:2 . . . . and can be considered a variant of SEQ ID NO:2."

As discussed, claim 1, as amended, recites that the claimed thermophilic enzyme having β-glycosidase activity "forms a tetramer, in which each subunit of the tetramer comprises the

amino acid sequence of SEQ ID NO:2." In contrast, the cited Ladrat *et al.* publication describes a thermostable β-glucosidase that forms a homodimer (see, *e.g.*, abstract). Thus, as the cited Ladrat *et al.* publication does not describe each and every element of claim 1, Ladrat *et al.* cannot anticipate claim 1 or depending claim 2. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. §102(b) over Ladrat *et al.* (J. Mar. Biotechnol. 4:192 (1996)) be withdrawn.

As to new claims 12 and 13, which depend from claim 1 and, therefore, also can form a tetramer, Ladrat *et al.* do not describe such an enzyme. Thus, Ladrat *et al.* (J. Mar. Biotechnol. 4:192 (1996)) do not anticipate new claims 12 and 13.

CONCLUSION

Applicants submit that all of the claims are now in condition for allowance, which action is requested. Filed herewith is a Petition for Automatic Extension with the required fee. Please apply any other charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

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APPENDIX A